Epitomes

Important Advances in Clinical Medicine

Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in pathology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.

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Immunohistochemistry and the Diagnosis of Spindle Cell Neoplasms

THE HISTOLOGIC DIAGNOSIS of poorly differentiated or unusual neoplasms by traditional methods may be difficult, relying on routine paraffin-embedded, hematoxylin-eosin-stained tissue sections augmented by special stains or ultrastructural examination or both. Recent advances in immunohistochemistry have added another dimension to tumor evaluation, giving immunologic clues to the diagnosis and decreasing the volume of cases previously examined by electron microscopy.

The antibodies generally used in immunohistochemistry are myriad, directed against structural "intermediate filaments" (keratin, vimentin, desmin, neurofilaments and glial fibrillary acidic protein), enzymes (such as neuron-specific enolase), other proteins (such as factor VIII, S-100) and other material. The literature, replete with immunologic characterization of various tumors, shows that few, if any, antibodies that have been developed are actually "specific" to a particular tumor. Despite this, immunohistochemistry is a powerful tool, especially when used to answer specific questions or to narrow a differential diagnosis formulated by review of more traditionally prepared material.

For example, the differential diagnosis of a spindle cell neoplasm arising in deep soft tissues and growing in long, sweeping fascicles includes fibrosarcoma, synovial sarcoma, leiomyosarcoma and malignant schwannoma. A battery of immunoperoxidase stains would show vimentin positivity in each because all are felt to be of mesenchymal origin. Of the four, only synovial sarcoma expresses cytokeratins—a finding similar to only three other mesenchymal tumors: mesothelioma, epithelioid sarcoma and adenomatoid tumor. The smooth muscle-derived leiomyosarcoma generally expresses desmin, whereas malignant schwannoma, being of neural crest derivation, reacts for S-100 protein. If all of the stains were negative (except for vimentin) then fibrosarcoma would be seriously considered.

The differential diagnosis of spindle cell tumors that occur more superficially in the subcutis or cutis includes melanoma, squamous carcinoma and several mesenchymally derived neoplasms including dermatofibroma, dermatofibrosarcoma protuberans, leiomyoma and leiomyosarcoma. Melanoma may be distinguished by its expression of S-100 protein and vimentin, while epithelial-derived squamous carcinoma produces only cytokeratin. The smooth muscle tumors show desmin and vimentin positivity whereas histiocytic markers such as α_1-antitrypsin, lysozyme and α_1-antichymotrypsin are generally found in dermatofibroma and dermatofibrosarcoma protuberans.

As techniques improve and antibodies are developed that are more tumor-specific, immunohistochemistry will become an even more powerful tool, improving the reproducibility of diagnosis in these and other difficult tumors.

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Barrett's Esophagus

BARRETT'S ESOPHAGUS is the eponym for replacement of the squamous epithelium of the distal esophagus by columnar epithelium. This replacement is now considered to be an acquired metaplasia that follows the epithelial injury caused by chronic gastroesophageal reflux and can therefore often be associated with strictures or peptic ulceration of the esoph-

agus. The exact prevalence is not known, but Barrett's esophagus is found in about 10% of patients undergoing esophagoscopy for symptoms of reflux.

On histologic examination, Barrett's esophagus has a heterogeneous appearance and comprises a variety of cell types similar to gastric and intestinal epithelial cells. A distinctive histologic pattern of goblet cells interspersed among columnar mucous cells is common and virtually diagnostic of Barrett's esophagus. Other patterns resemble gastric fundic or cardiac mucosa and can thus be interpreted as Barrett's esophagus only when the site of biopsy is definitely the esophagus and not a hiatus hernia.

This condition is clinically important because of its association with esophageal adenocarcinoma. In recent studies, a 30 to 40 times increased risk was estimated when Barrett's esophagus is present. Because these figures are based on a relatively short follow-up period, the actual risk may be even higher. Such considerations have led to the suggestion that biopsies be done regularly on patients with Barrett's esophagus to look for epithelial dysplasia, which, as a putative precursor of adenocarcinoma, would serve to identify those patients at highest risk for malignancy. Problems with this suggestion include the lack of well-defined histologic criteria for recognizing dysplasia and distinguishing it from reactive or regenerative changes. Nevertheless, high-grade dysplasia has recently been shown to represent a morphologic marker of risk for esophageal adenocarcinoma.

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The Carcinoma-Carcinoid Spectrum

IN THE PAST DECADE we physicians have become aware that carcinoid tumors show a much wider clinicopathologic spectrum than previously thought. This has given rise to a plethora of new terms, some of which, such as apudoma, neurochristoma and neuroendocrinoma, are based on their postulated neuroectodermal derivation; others, such as neuroendocrine carcinoma, on their clinical behavior, and a group, such as gastrinoma, on their secretion products. Because these tumors are morphologically distinctive, I see no point in changing Obendorfer's original terminology, and thus I designate these lesions as carcinoids and specify their differentiation and secretion products (Table 1).

On histologic examination, some tumors may show atypical features such as glandular profiles, a spindle cell pattern, squamous or osteoid metaplasia or pleomorphism with frequent mitoses and necrosis. In rare cases they may be poorly differentiated and resemble undifferentiated large-cell or small-cell carcinoma (oat cell carcinoma) and lymphoma. As is well known, some carcinoids are associated with well-defined syndromes, such as the carcinoid or the Zollinger-Ellison syndromes, due to the secretion of amines or peptides. Immunohistochemical analysis of these tumors has shown that, whereas one amine or peptide may predominate, such as serotonin or gastrin, most are multihormonal. These findings

TABLE 1.—*Nomenclature and Classification of Pure and Mixed Endocrine Cell Tumors*

Carcinoid tumors
Well differentiated
Moderately differentiated
Poorly differentiated
Small cell (oat cell)
Large cell
Mixed (composite) glandular-endocrine cell carcinoma
Microglandular-goblet cell carcinoma
Scirrhous-argyrophil cell carcinoma
Adenoendocrine cell carcinoma
Amphicrine cell carcinoma

are also seen with the clinically silent carcinoids such as the foregut and hindgut tumors. Furthermore, the immunohistochemically shown amines and peptides in the primary tumor do not necessarily correspond to those found in the overlying endocrine cells or in metastatic lesions.

Although the presence of scattered endocrine cells within adenomas and carcinomas of the gastrointestinal tract has been known for some time (in as many as 20% of all colonic carcinomas), there are a number of tumors in which there is a large admixture of endocrine and epithelial cells. Thus, the strict separation of gut mucosal tumors into carcinoma and endocrine tumors has had to be modified to include those tumors with admixtures of varying proportions of endocrine and epithelial cells. These tumors have been designated as mixed or composite tumors and have been further subdivided into several distinctive histologic types (see Table 1). Some of these tumors, such as the microglandular-goblet cell carcinoma, have a distinctive clinical behavior, whereas others, such as the scirrhous-argyrophil and adenoendocrine cell carcinoma, appear to behave in a manner similar to the corresponding carcinoma. Finally, there is a further distinctive tumor type, namely the amphicrine tumors. These differ from the mixed tumors in that endocrine and epithelial cell constituents are present within the same cell. These findings support the hypothesis that epithelial and endocrine cells of the gut share a common cell of origin.

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Lymphocyte Gene Rearrangements—A New Technique in the Diagnosis of Lymphoma

THE HISTOPATHOLOGIC DIAGNOSIS of lymphoma can be difficult, particularly when the disease presents at extranodal sites. Conventional microscopic or immunohistochemical studies often prove inadequate for the evaluation of T-cell infiltrates, of neoplasms lacking appreciable atypia or where a superimposed inflammatory process obscures the underlying malignant process.

Recent insights into the molecular biology of lymphocytes have led to the development of a technique that provides an objective estimate of the clonal composition of lymphoid in-